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DIRECTOR OF MEDICAL SERVICES, A.L.F., S.E.A.

TECHNICAL MEMORANDA—SECTION "D"

PATHOLOGY.

MEDICAL DIRECTORATE,
ALLIED LAND FORCES,
SOUTH-EAST ASIA.

MEMORANDUM NO. 9. *Dated* 11 JAN. 45

PENICILLIN.

T. O. THOMPSON,
Major-General,
D.M.S., A.L.F., S.E.A.

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"Anything green that grew out of a mould,
Was an excellent herb to Our Fathers of Old"

—*Rudyard Kipling.*

PENICILLIN.

General Information and Notes on its Use.

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PENICILLIN.

General Information and Notes on its Use.

1. Historical.

The following are the chief events leading up to the discovery and use of Penicillin:

1877—Pasteur observed that certain airborne organisms inhibited the growth of the anthrax bacillus.

1899—Emmerich and Loew extracted from B. pyocyaneus 'pyocyanase,' an effective antibiotic against anthrax and diphtheria.

1922—Fleming described 'lysozome,' a powerful natural anti-bacterial ferment found in human secretions, and elsewhere.

1924—Fleming demonstrated the anti-leucocytic power of anti-septics.

1929—Publication of original paper by Fleming describing the discovery of Penicillin the year before, its uses in the laboratory and some clinical observations.

1940—Chain and Florey isolated the active principle and described animal experiments at Oxford.

1941—Publication of more exhaustive paper and clinical trials by the Oxford workers.

1942-43—Clinical trials under active service conditions conducted by the War Office and M.R.C. in the Middle East and Italy.

2. Penicillium Notatum (Westling).

P. notatum is the mould from which the anti-bacterial substance penicillin was originally isolated.

Occurrence.—P. notatum is a species of the common genus Penicillium, which occurs widespread on organic material. It rots fruit, attacks meat and vegetables, contaminates media, etc. Penicillium moulds are used in industry, *e.g.*, for ripening cheeses. About 150 species are known.

The species P. notatum has been used as a selective agent in bacteriology since 1929.

Morphology.—The gross appearance is that of a bluish green mould, like that seen on Stilton cheese—a species of the same genus. The vegetative mycelium consists of a complex network of branching, thin-walled, septate hyphæ. The characteristic of the genus is the ' penicillus ' or a sexual reproductive organ.

Cultivation.—P. notatum will grow and produce penicillin on a variety of media, including simple broth. The mould is strongly aerobic. It forms a heavy wrinkled felted belt on the surface of the medium. The yield of penicillin varies with the medium.

The optimum temperature for growth is 24° C. None is produced at 37.

P. notatum yields two anti-bacterial substances—penicillin and notatin.

3. Penicillin.

Chemical and Physical Properties.—Penicillin is a complex substance of unknown chemical structure. It occurs naturally as an unstable acid. In the form of alkaline earthy salts, it is stable between pH 5 and 7. Preparations used therapeutically are the calcium and the sodium salts.

The molecule is small—this may be related to its rapid excretion. Penicillin is soluble in ether, chloroform, and amyl acetate. The salts are extremely soluble in water.

It is destroyed by dilute acids, alkalis and prolonged heating.

It is inactivated by oxidising agents, procaine, heavy metals (especially zinc, cadmium, copper and mercury), primary alcohols, ketonic reagents, and enzymes produced by certain bacteria.

In the dried state, the anti-bacterial activity remains unchanged for a long time. Activity lasts longer at low temperatures (below 10°C).

Pure penicillin would have an activity of about 1000 units per milligramme. Commercial products are at present only 30—50 per cent pure. Material with a potency of a 100 units per milli-

gramme or less is satisfactory for clinical purposes. Impurities consist mainly of pyrogens.

Biological Properties.—In the presence of penicillin, even in low concentration, certain species of bacteria not only cannot multiply but slowly die.

This effect is exerted as well in serum, blood or even pus, as it is in a simple medium such as broth. It is independent of the number of bacteria present. Even in high concentration, penicillin has no effect on the leucocytes.

In contrast, the sulphonamides are toxic in high concentration, act best in the presence of few bacteria, and are inhibited by the breakdown products in pus. It is now established that penicillin and sulphonamides acting together produce an enhanced effect.

Most of the susceptible species are gram positive. They include the three main pyogenic cocci (Staphylococcus aureus, Pneumococcus and Streptococcus pyogenes), the gas gangrene group, B. anthracis and C. diphtheriæ.

The only fully susceptible gram negative species are Neisseria, the gonococcus and meningococcus.

Among resistant organisms are the tubercle bacillus and almost all gram negative bacilli including the coli-typhoid-dysentery group, the genera Brucella and Hæmophilus, and two common invaders, B. Proteus and B. Pyocyaneus. Penicillin is useless for tuberculosis, dysenteries, typhus, protozoal infections and virus diseases.

Penicillin Sensitive Bacteria.	**Penicillin Resistant Bacteria.**
Staphyloccocus.	Typhoid, Paratyphoid, Dysentery coli group.
Streptococcus pyogenes.	V. choleræ.
Other hæmolytic streptococci, (other than Group D).	Friedlander's bacillus.
Streptococcus viridans.	B. pyocaneus.
Non-hæmolytic streptococci (most).	B. proteus.
Pneumococcus.	Brucella.
Gonococcus.	B. pestis.
Meningococcus.	Enterococcus.
M. Catarrhalis.	Non-pathogenic gram-negative cocci of the respiratory tract.

Diphtheria bacillus.
Diphtheroid bacilli (most).
Anthrax bacillus.
Actinomyces.
B. welchii and other clostridia.
Tubercle bacillus.
Yeasts.
Moulds.

Treponema pallidum.
*Spirillum minus.
*Leptospira icterhæmorrhaghiæ.

* Further information is required regarding the alleged sensitivity of these organisms.

Absorption.—Penicillin is absorbed rapidly from muscle and wounds, slowly from subcutaneous tissue. It is absorbed from the small intestine, but not from the mouth or rectum.

After intramuscular or intravenous injection, penicillin can be detected in the urine almost immediately, and it persists for 6 to 24 hours. There is an immediate rise in blood concentration to a peak, followed by a rapid fall. Bacteriostatic concentration in the blood is maintained for about 3 hours after injection of amounts used therapeutically (15,000 units).

Passage of penicillin between the blood stream and serous cavities seems slight and little gets into the C.S.F. following intramuscular or intravenous injection. After intrapleural injection, penicillin can be demonstrated in the urine after one hour.

Excretion.—Penicillin is excreted rapidly by urine (which is stained yellow), by bile and by saliva. This rapid excretion has been likened by Florey to 'trying to fill a bath with a plug out.' Hence the need of frequent injections to maintain a bacteriostatic level in the blood.

Over 75 per cent of the penicillin injected into blood or muscle is excreted unchanged. One half can be recovered. The yield from urine is variable owing to the destruction of penicillin by bacteria in the urine. It is not known whether the total amount given is excreted or whether part is destroyed in the body.

The kidneys have the power of concentrating penicillin. After a single dose it can be detected in the urine for over 24 hours, even when the concentration in the blood is insufficient to be detected by present methods. Hence administration for urinary infection has been successful when repeated only once or twice in 24 hours.

Toxicity.—It is said that penicillin is completely non-toxic. An occasional rise in the blood urea has been observed, but this

has fallen immediately on discontinuing treatment. A rise of temperature following penicillin is probably due to the absorption of bacterial degradation products.

4. Penicillinase.

Penicillinase is an enzyme which inactivates penicillin. It is isolated from the bodies of coliform organisms, paracolon bacilli, B. pyocyaneus, A. bovis and certain airborne organisms. Contamination of penicillin solutions with penicillinase producing organisms destroys the penicillin. Its mode of action is unknown. Penicillinase producers are usually insensitive, but not always.

This property of certain organisms not only to survive and multiply in solutions of penicillin, but also to produce penicillinase, calls for high standards of precaution in handling during preparation, and exceptional safeguards during subsequent use. (Garrod).

Penicillinase is used bacteriologically to assist in the isolation of organisms from blood, pus, C.S.F. and exudates of patients under treatment.

5. Notatin.

This is a second anti-bacterial substance produced under certain conditions by P. notatum. It is not soluble in such organic solvents as ether and therefore is not found in purified commercial products today.

Notatin (also called ' penicillin B ' or ' penatin ') forms hydrogen peroxide in the presence of glucose. It has no action in the absence of glucose, nor in the presence of catalase, a constituent of all tissue cells. It is toxic to animals. It is an effective anti-bacterial agent in vitro, being particularly effective against gram negative organisms which are not sensitive to penicillin.

Its presence in crude extracts of penicillin must be borne in mind by the bacteriologist, and media containing glucose should not be employed in the assay of such extracts.

6. Commercial Preparation.

Penicillin has not been synthesised. It is labile and cannot be sterilized. Hence the difficulty in commercial preparation.

A high potency strain of P. notatum is selected and preserved as a stock culture in the frozen state. Subculture is made on to a

Sabouraud slope, from which a number of Roux bottles containing a fluid medium are inoculated.

Incubation at 24°C is maintained for 7-14 days. White cottony vegetative patches form on the surface and spread to form a thin mat. This is replaced by green spores about the sixth day. Penicillin and a yellow pigment 'chrysogenia,' exude into the fluid. With increased age, the pellicle wrinkles and shows innumerable convolutions.

By periodically assaying the liquid for penicillin production, it is possible to harvest the batch at the time of peak penicillin accumulation. The liquid medium is separated from the mould by filtration and extracted with organic solvents. The final product is obtained as an aqueous solution of alkaline salt. This orange coloured solution is frozen and dried in vacuo, yielding the powder used clinically.

The powder is very soluble in water and subject to deterioration if exposed to high temperatures, or even room temperature for prolonged periods.

Potency is expressed in terms of the 'Oxford Unit,' which is an arbitrary amount determined by comparison with a standard preparation. The present standard is a barium salt, which is very stable. The 'substandard' in use for assay in India contains 58.5 units per milligramme. The potency of the 'Oxford Unit' is such that 0.01 to 0.02 of a unit per c.c. completely inhibits the growth of strains of a staphylococcus—the 'Oxford' staphylococcus. A Mega unit is equal to one million Oxford units.

The sodium salt now available, is packed in ampoules/bottles containing 100,000 units. 10 to 12 ampoules are packed in each carton.

7. Storage and Keeping Qualities.

Ampoules should be stored below 10°C (50°F). Under these conditions the drug keeps perfectly until its expiration date, which at present is 3-6 months from the date of testing and filling. The material is not damaged by extremely low temperatures. The administration of outdated products causes no ill effect, since the only change which occurs is a diminution of potency.

Although there is every reason to believe that penicillin of U. S. manufacture retains its advertised unitage for several months beyond the labelled expiry date, storage under suboptimal condi-

tions may result in an unpredictable loss of potency. It is therefore advisable to assay stocks from time to time. If deterioration has occurred, the unitage as determined by assay should be accepted in prescribing dosage.

Once made up in solution, penicillin preparations begin to lose potency. Solutions must therefore be taken from the refrigerator for actual application only, being returned immediately to the cold after use. This must be stressed regularly to the ward staff. Not more than estimated requirements for 24 hours should be prepared at one time.

Knowledge regarding keeping qualities of penicillin is still imperfect.

8. Dispensing.

Meticulous attention to absolute sterility in making up preparations for local and parenteral use is essential. Many common contaminants, not only grow freely in penicillin but destroy the drug, besides contaminating the wound. All preparations will therefore be made up in the laboratory or the theatre by a **Medical Officer.**

Solutions may be made up in sterile distilled water (pyrogen-free if for intravenous use), in sterile isotonic sodium chloride, or in 5 per cent dextrose solution.

Solutions will be made up in autoclaved bottles. The following bottles are suitable for the purpose; and may be obtained on indent from dependent medical stores or from the nearest laboratory in an emergency.

P.V.M.S. No. 16104 Bottle media N.M. 6 oz. screw-capped.
,, ,, 16106 ,, ,, ,, 2 ,, ,, ,,
,, ,, 16108 ,, ,, ,, 1 ,, ,, ,,

Note.—It is now established that certain brands of synthetic rubber are harmful to penicillin, and certain batches of glucose saline may be acid in reaction with pH between 3 and 5, which may cause its deterioration. It is therefore necessary that glass bottles, tubes and rubber fitments should be tested in Laboratories to discover whether or not they give off alkaline or acid substances.

For Systemic Administration.

A convenient method of preparation is to dissolve the contents of one ampoule (100,000 units) in 40 c.c. of sterile distilled water. This results in 8 doses of 12,500 units each dissolved in 5 c.c. This is sufficient for one day's requirements.

When larger doses of penicillin are to be administered as in syphilis, adopt the following procedure :—

Take 10.5 c.cs of distilled water in a 10 c.c. syringe, and transfer to a bottle of penicillin powder containing 100,000 units. Dissolve by gentle shaking. (Avoid frothing, as this leads to a considerable loss of penicillin as the solution cannot be easily aspirated). Aspirate contents and discharge in a second bottle of penicillin. Dissolve as above. The second bottle now contains 200,000 units in 10 c.cs. This gives 5 doses of 40,000 units each in 2 c.cs volume.

For local use.—Solutions containing 250-1,000 units per c.c. are commonly used. Solutions should be discarded after 72 hours. 3-5 c.c. or more are required for irrigation according to the nature of cavity.

For the preparation of creams and powders, the calcium salt which is not hygroscopic, is required. The sodium salt is not suitable for this purpose. The usual vehicle for the preparation of powders is sulphanilamide or sulphathiazole, with 5 per cent sterile magnesium oxide to prevent caking. Powders commonly contain 250-5,000 units per gramme.

For creams—lanette wax alone or with soft paraffin or ol. arachis is used. 100-1,000 units of the calcium salt per gramme is used. The following is a convenient formula :—

Lanette wax 4 per cent.
Liq. paraffin 25 per cent.
Paraffin wax 3 per cent.
Penicillin solution in water 68 per cent.

Further instructions regarding the preparation of creams and powders will issue when the calcium salt becomes available.

9. Routes of Administration and Dosage.

Intramuscular route.—This is the route of choice for parenteral administration. The injection is given deep into the muscles of the thigh (*vastus externus*), the gluteus (upper and outer quadrant of the buttock) or the deltoid. This is the order of choice in bed-ridden patients.

The standard course of treatment is 12-15,000 units (dissolved in 5 c.c.) every three hours for 7 days. Continuous intramuscular drip into the thigh muscles has been tried but has not proved as effective as was hoped.

There may be a transient burning pain at the site of injection, but this passes off after a few doses. The pulse rate, the general condition and the feeling of the patient and the results of culture, give an indication of progress.

Intravenous route.—The frequent occurrence of thrombosis or thrombophlebitis after intravenous injection of penicillin renders this route undesirable.

Intrathecal.—Penicillin passes sparingly into the spinal fluid. In meningitis it must be given intrathecally. The dose recommended is 5-10,000 units once or twice daily. The cell count may rise as a result, and there may be headache and vomiting.

Syringes.—Glass syringes are not recommended, as it is almost impossible to avoid contamination of the wide plunger by the hand when withdrawing it. Record syringes of 10 and 20 c.c. capacity are satisfactory; the detachable metal guard for the top of the syringe should not be fitted, so that any solution leaking past the piston can drain away freely.

Pleural and joint spaces.—For injection into empyema and other abscess cavities, including purulent joints, a concentration of 1,000 units per cubic centimetre of normal sterile saline or distilled water may be used.

Local.—A considerable saving of penicillin can be effected by shifting from systemic administration to local application. Solutions containing 250 units per c.c. of sterile distilled water or normal saline are usually used. The concentration may be increased to 500 units in the case of resistant infections. The solutions may be applied to the wound surface in the form of wet dressings or introduced into the wound cavity by means of tubes. Wound cavities may be irrigated through the tubes three or four times daily as required. To prevent the escape of fluid through the tubes they may be closed by means of spring clips or spigots.

Dosage.—It is advisable to give penicillin in adequate dosage early in treatment, organisms, especially staphylococci, are known to become "penicillin-fast" when subjected to small doses given over a long period of time.

The patient's general condition and the local state of the lesion are the opsonic indices of the success or otherwise of the therapy. In this connection, the temperature is probably the least significant evidence; for a raised temperature may persist almost throughout the whole course though the patient and his lesions are obviously doing well.

The penicillin administration should be continued for 3-4 days after the temperature is normal, or the local lesion is shown to be free from sensitive organisms; the treatment should be discontinued if secondary infection with coliform organisms or pyocyaneus occurs.

The average total dosage necessary is extremely variable, running from 100,000 units in simple gonorrhœa, to 400,000 units in severe infections. As large a dose as 600,000 units has been given in 24 hours without harmful effect.

For further details regarding both local and parenteral administration *see* paras 12 and 13—"Notes on Some Special Conditions."

10. Laboratory Control.

Except in emergency, and in forward areas where laboratory facilities are not available, it is rarely justifiable to treat any case with penicillin without making a bacteriological diagnosis, since the outcome depends so much upon the nature of infection. The majority of pathologists are now in a position to advise on the penicillin sensitivity of particular infections, and know how to determine the actual penicillin content of various preparations and body fluids.

During treatment it may be necessary to confirm the potency of the penicillin used, to measure the amount of penicillin present in the blood or other body fluids, and to determine whether the infecting organisms have developed alterations in sensitivity or if secondary infection with other organisms has complicated the picture.

For these reasons, a close liaison between the ward and the laboratory is essential, not only at the commencement of treatment, but throughout the course.

The pathologist should also give advice and teaching regarding the preparation and care of penicillin preparations.

Where the potency of a batch of penicillin is suspected, samples should be sent to a reference laboratory for assay. Facilities for this exist at 26, Ind. Field Laboratory, Comilla, in the case of Fourteenth Army, 15 Corps, and L. of C. Command, and 35 B.G.H. for Ceylon Army Command.

11. Reactions.

The following reactions thought to be due to penicillin, have been described :—

(*a*) **Urticaria.**—This may occur at any time in the course of treatment and may be associated with fever and abdominal cramps. The course is unaffected by continuation or cessation of treatment. Therapy may usually be continued through the period of urticaria, and subsequent courses of treatment are not contra-indicated.

(*b*) **Thrombophlebitis.**—This may occur within 12 hours. It may be accompanied by chills and fever, if therapy is continued through the same vein.

Other reactions which have been noted include the following. They are thought to be due to impurities and are getting less as the purity of commercial products improves :

(*a*) Eosinophilia—as high as 20 to 30 per cent.
(*b*) Burning pain at the site of injection. This only occurs during the first 48 hours of treatment as a rule.
(*c*) Headache.
(*d*) Faintness and flushing of the face.
(*e*) Unpleasant taste following parenteral injection.
(*f*) Tingling in the testes.
(*g*) Muscular cramps.

12. General Principles governing Treatment with Penicillin.

THERE IS A TENDENCY WHEN ANY NEW DRUG SUCH AS PENICILLIN IS GIVEN TO FORGET THE WELL ESTABLISHED MEDICAL AND SURGICAL PRINCIPLES AND PROCEDURES. IT CANNOT BE TOO STRONGLY EMPHASISED THAT THE PATIENT STILL NEEDS MENTAL AND PHYSICAL REST, AND SLEEP, AND FIRST CLASS NURSING ; HE STILL NEEDS FOOD AND WATER IN PROPER AMOUNTS—

ON NO ACCOUNT MUST HE BE ALLOWED TO GET WASTED OR DEHYDRATED—,HE STILL NEEDS RELIEF FROM PAIN; HE MAY STILL NEED TRANSFUSIONS OF BLOOD OR PLASMA; HE MAY STILL NEED ANTITOXIC SERA OR DRUGS FOR CONCOMITANT DISEASES SUCH AS MALARIA. ON NO ACCOUNT MUST THE GENERAL CARE BE RELAXED SIMPLY BECAUSE PENICILLIN IS BEING USED.

The properties of penicillin-bacteriostasis, absence of toxicity and activity in the presence of blood and pus make it an ideal antiseptic. It can therefore be used in any local or systemic infection, provided that :

(*a*) The organism is a sensitive one.

(*b*) The dosage is effective and sustained.

(*c*) The drug can be given access to all the infected tissues.

(*d*) Rigid asepsis in preparation and administration of solution is maintained.

It can be used in two principal ways :—

(1) To prevent infection—This is the principle underlying its early use in war wounds.

(2) To eliminate established infection by sensitive organisms. This may be effected by **systemic administration** in the case of septicæmia, and in the case of local lesions to which the drug has access—*e.g.*, wounds of soft tissues, urethral infections, pulmonary infections, etc. Barriers of granulation tissue, and selerosed bone deny adequate access ; hence it is less useful in chronic bone infections, and cannot be expected to sterilise a wound in which sequestra, and which contains infected foreign bodies.

Local administration to the site of infection will remove penicillin sensitive organisms provided the application is efficient, and there are no penicillin resistant organisms present.

It is obvious that a combination of systemic and local administration will be called for in many cases, and that wherever possible, an attempt should be made to determine the precise nature of the infection, and the bacteriology of the wound or infected tissue.

Selection of cases for Penicillin Treatment.—The following order of priority is recommended :—

(*a*) Battle casualties.

(*b*) Severe infections due to penicillin sensitive organisms.

(*c*) Skin, ear and eye infections due to susceptible organisms.

(*d*) Venereal infections.

(*e*) Other appropriate medical conditions.

It is emphasised that cases must not be held forward or their evacuation delayed for penicillin therapy, **if they are fit to travel.** There are neither sufficient beds, nor adequate nursing facilities for sustained penicillin treatment in forward areas, except for serious cases unfit for evacuation.

13. Notes on some special conditions.

Septicaemia.—Penicillin is valuable in septicæmia especially when staphylococcal, streptococcal or pneumococcal.

Dosage—15,000 units 3 hourly for 3 days, then 4 hourly for four days.

An initial dose of 25,000 units may be advisable in some cases. Hæmolytic Streptococci are practically always more sensitive to penicillin than are staphylococci.

Acute osteomyelitis, septic arthritis, septic gunshot wounds.

If septicæmia is present, the dosage is as above. Surgery is always required in infection of the long bones, but there is some evidence that flat bones can manage without, unless there are sequestra. Local therapy is an effective supplement.

Tubes should not be introduced into closed cavities such as joints. Repeated aspiration of pus and replacement with penicillin, 1,000 units per c.c. is recommended.

Compound fractures.

Penicillin does not invariably prevent or cure infection but in the majority of cases marked local and general improvement results from its administration.

Gas Gangrene.

Penicillin definitely helps to control the spread of gas gangrene and is said to reduce the toxæmia considerably. It does not reduce the necessity for major surgery, nor for anti-toxin which must be given as directed.

Initial dosage is larger than usual, 22,500 units is given intramuscularly 3 hourly instead of 15,000. The course lasts 3 to 5 days.

Anti-gas gangrene serum should be given before operation. 50,000 units of polyvalent serum is given intravenously and repeated every 6 to 8 hours. Penicillin takes about 36 hours to act fully, during which time the patient appears to go down hill, with an increase of crepitus and œdama. Then quite suddenly in the course of an hour or two the moribund patient becomes rational and a marked improvement ensues. During the "depressed" phase, blood transfusion is most important.

Empyema.

Parenteral penicillin does not reach serous cavities. In empyema it should be given locally after each aspiration in a dose of 30,000 to 60,000 units according to the size of the empyema. This will usually sterilise the pus, but rib resection is often necessary for drainage and evacuation of clots and fibrin.

Pneumonia.

Penicillin is the drug of choice in streptococcal or staphylococcal pneumonia. Large doses may be required. For pneumococcal pneumonia, if sulpha drugs are not effective in 72 hours, penicillin in normal parenteral dosage should be given.

The drug is ineffective in a typical pneumonia.

Small Pox.

Secondary infection of pox is usually staphylococcal. 100,000 units a day given intramuscularly for 3-4 days may control septic complications.

Ophthalmic cases.

There are three established methods of administering penicillin in ophthalmic cases :—

(*a*) Systemically, by parenteral injections. This under present conditions is only indicated in extremely severe cases not responding to local treatment, *e.g.*,

threatened panophthalmitis. The dosage and technique do not differ from what is applicable in general surgery.

(*b*) Locally, by irrigating the anterior chamber with a sterile aqueous solution containing 500-1,000 units per c.c. (Recent reports from another front suggest that penetrating power through an abraded cornea of penicillin in drops or ointment applied locally is such that anterior chamber irrigation is seldom necessary).

(*c*) By surface application in the form of :—

(*i*) Drops—sterile aqueous—250 units per c.c. two drops are placed in the lower fornix every 4 hours.

(*ii*) Ointment. 30 per cent lanette wax (Sx. quality) in water—penicillin added to make 250 units per gram.

N.B.—Lanette wax is not yet available in India and some reports suggest that the effectiveness of penicillin in this form deteriorates more rapidly than in sterile aqueous solution under adequate conditions.

Penicillin has proved effective in the following four groups of ophthalmic conditions. The average time in which cure was obtained in a recent investigation in U. K. is given in brackets.

(*a*) Severe conjunctivitis. (5 days).

(*b*) Severe conjunctivitis with marginal or superficial Keratitis. (7½ days).

(*c*) Severe conjunctivitis with corneal ulcer (9 days).

(*d*) Severe or chronic blepharitis (14 days—some case resistant).

Swabs should be taken before treatment is initiated, and daily until 2 consecutive negative swabs are obtained, also on any sign of a relapse during treatment. In the event of treatment not proving effective within a reasonable time, a test of the organism for penicillin-sensitivity is indicated. Should the organism prove to be sensitive, a useful check on the efficacy of the penicillin solution is thereby obtained.

Treatment should be continued for 7 days after the first negative swab is obtained. Allowing for wastage, approximately 5,000 units on the above basis are required to treat bilateral case for 10 days.

14. Venereal Diseases.

Syphilis.—A separate memorandum will be issued.

Penicillin in the treatment of Gonorrhoea.

The following treatment is recommended for cases of acute and chronic gonorrhœa.

(*a*) All cases will be diagnosed microscopically by identification of the gonococcus stained by Gram's method.

(*b*) **Treatment.**

	TIME.				
	0900 hrs.	1200 hrs.	1500 hrs.	1800 hrs.	2100 hrs.
Day 1—Sulphathiazole ...	2 gms.	1 gm.	1 gm.	2 gms.	2 gms.
Day 2— ,, ...	1 gm.	1 gm.	1 gm.	1 gm.	...
Penicillin ...	15,000 units	15,000 units	15,000 units	15,000 units	15,000 units

Note 1. A minimum of 8 pints of fluid will be given daily.

Note 2. Alkalis in large dosage will be given for the first 48 hours.

Note 3. The tablets will be crushed and given as a powder and one pint of water taken afterwards.

Note 4. The penicillin will be dissolved in sterile distilled water—10,000 units to 1 c.c. Each injection will be given by the intramuscular route.

Note 5. It must always be remembered that this amount of penicillin may mask an early case of syphilis.

Note 6. A W.B.C. will be done on all cases who have had previous chemotherapy.

(*c*) **Tests of cure.**

A new drug is being employed and in order to assess its efficiency, tests of cure will be rigid.

These laid down in " Notes on the Treatment of Venereal Diseases " No. 7170/D.M.S. 5(*c*), G.H.Q. (I), 1944, will be carried out. These are again repeated for information.

1. Before discharge from hospital.

(*a*) No evidence of urethral discharge 48 hours after the cessation of treatment.

(*b*) Urine clear from threads in both glasses using the 2 glass test 48 hours after treatment.

2. After discharge from hospital.

The Unit M. O. will examine the patient week by week for 3 weeks and ascertain :

(*a*) That there is no evidence of urethral discharge.

(*b*) That the urine is free from threads.

3 months after discharge from hospital the patient will attend the nearest specialist in venereology who will perform the following tests of cure :

(*a*) Ascertain there is no urethral discharge.

(*b*) Ascertain the urine is clear by the 2 glass test.

(*c*) Examine the prostate and examine the prostatic and vesicular secretions microscopically.

(*d*) Pass a curved sound.

(*e*) Do a urethroscopy (if urethroscope available).

The A.F.M. 1272 will then be completed and the man struck off the local register and his unit notified.

Disposal of I.A.F.M. 1272.

On the completion of surveillance the hospital completing treatment will w.e.f. January 1945, forward them in batches to the Adviser in V.D., Advance H.Q., Allied Land Forces, S.E.A.C.

15. Penicillin Officers.

A senior medical officer will be appointed by name to be responsible for the control of Penicillin therapy in each medical unit where it is used. This Officer will normally be the Officer in charge, surgical divisions, or a surgical specialist. The duties of this Officer will include the following :—

(*a*) To ensure that the drug is properly stored and secure against theft.

(*b*) To decide whether a case is suitable for Penicillin therapy.

(*c*) To give technical instruction to nursing officers carrying out Penicillin therapy.

(*d*) To supervise the preparation of solutions, and be responsible for providing the necessary materials together with the method for preparation.

(*e*) To ensure that careful clinical records are maintained for all cases on Penicillin treatment in the unit.

Training.—Training of Unit Penicillin officers will be carried out at the main Penicillin centres ; they will be responsible for the subsequent education of other medical officers of the Unit.

16. Reports.

All medical units which can do so will arrange to study the action of Penicillin in groups of infections where clinical material is available. This is especially indicated where the experimental evidence of the value of the drug is inconclusive. Such cases should be carefully studied. Accurate, clear and concise records will be kept, and summaries drawn up periodically. All medical units using penicillin may be called upon to furnish reports from time to time on the results of treatment.

In cases of particular interest, or in cases where penicillin treatment fails to produce the beneficial effect to be expected after a course of adequate dosage, a brief report will be submitted and forwarded through the usual channels.

17. Publications and acknowledgments.

These notes are based on the following publications :—

Director of Medical Services—Middle East Administrative Instructions, 1944, Dated 30th of July, 1944.

British Medical Bulletin, Vol. 2 (1944), No. 1.

U. S. War Department Technical Bulletin, T. B. Med. 9.

Current Medical Literature.

Medical Directorate, India, Bulletin No. 25, para 197 (from A. M. D. Bulletin 30).

Army Medical Department Bulletin No. 16.

Medical Directorate, India, Administrative Instruction No. 76, Dated 28th April, 1944.

G.H.Q.(I) letter No. 19879/D.M.S. 10(*a*), Dated 28th February, 1944—"The Properties and Action of Penicillin."

British Medical Journals of the following dates :—

December 11th, 1943, p. 755 "Treatment of War Wounds with Penicillin." (Reprinted in Indian Medical Gazette, dated July 1944, P. 338).

April 15, 1944—"Report on Therapeutic Properties of Penicillin."

July 1st, 1944—"Penicillin in Battle Casualties".

August 5th, 1944—"Penicillin in Empyema," "Penicillin in Ophthalmology."

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